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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,263	01/09/2006	Charles A. Blum	60883(72021)	6999

21874 7590 11/17/2008

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EXAMINER	
SZNAIDMAN, MARCOS L	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
11/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,263	BLUM ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-9,11,16,27,28,31-34,39,43,44 and 48-51* is/are pending in the application.

4a) Of the above claim(s) *31-34, 39, and 43-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-9,11,16,27,28 and 48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9 pages/ 01/09/06, 02/21/06, 01/26/08 and 06/30/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on June 30, 2008.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-2, 5, 7-9, 11, 16, 48-51 and 27-28) and compound 2 (see specification, page 44, Table I) in the reply filed on June 30, 2008 is acknowledged. The traversal is on the ground(s) that there is no burden in searching all the groups together. This is not found persuasive because searching for: inhibition for binding of a vanilloid ligand to a capsaicin receptor in vivo (Group I), would not overlap with a condition like asthma (Group V).

The requirement is still deemed proper and is therefore made FINAL.

Since the elected species was free of prior art, the search was expanded to the remaining species which are also free of prior art.

Status of Claims

Amendment of claims 1 and 7 is acknowledged.

Claims 1-2, 5, 7-9, 11, 16, 27-28, 31-34, 39, 43-44, and 48-51 are currently pending and are the subject of this office action.

Claim 31-34, 39, and 43-44 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable

generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 30, 2008.

Claims 1-2, 5, 7-9, 11, 16, 27-28 and 48-51 are presently under examination.

Priority

The present application is a 371 of PCT/US04/21914 filed on 07/09/2004, and claims priority to provisional application No. 60/485,958 filed on 07/10/2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5, 7-9, 16, 48-51 and 27-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1-2, 5, 7-9, 16, and 48-51 recite a compound represented by the structure of claim 1, or a pharmaceutical composition comprising a comprising a compound of claim 1. Claims 27-28 recite a method for inhibiting binding of vanilloid ligand to

capsaicin receptor in vitro or in a patient, comprising contacting cells with a compound of claim 1.

M.P.E.P. #2163 states: "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention….one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

A description of a chemical genus will usually comprise a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the members of the genus, which features constitute substantial portion of the genus. See *Univ. of California vs. Eli Lilly*, 43 USPQ 2d 1398, 1406 (Fed. Cir. 1997). This is analogous to enablement of a genus under section 112 first, by showing enablement of a representative number of species within the genus. A chemical genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient number of species to reflect the variation within that genus.

Applicant has failed to show that he was in possession of all the diverse compounds encompassed by de general structure of claim1. Applicant discloses the specific structures of only 5 compounds (see specification, Table I, pages 44-45) all of

which show a very narrow set of substituents for Z, W, Y, Ar1 and Ar2 (for example Ar1 is either trifluorophenyl or trifluoropyridyl, Ar2 is a para substituted phenyl ring, and Z = W = Y = C-H). This small set of compounds can not be viewed as being reasonably representative of the genus in its claimed scope because no readily apparent combination of identifying characteristics is provided, other than the disclosure of those specific species as examples of the claimed genus.

Given the broad scope of the claimed subject matter, Applicant has not provided sufficient written description that would allow the skilled in the art to recognize all the compounds of claim 1 claimed.

Claims 27-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro* or *in vivo* with the compounds listed in Table I (see specification, pages 44-45), does not reasonably provide enablement for inhibiting binding of vanilloid ligand to a capsaicin receptor *in vitro* or *in vivo* with any of the other remaining compounds claimed in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without

undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention

Claims 27-28 recite a method for inhibiting binding of vanilloid ligand to capsaicin receptor *in vitro* or in a patient, comprising contacting cells with a compound of claim 1.

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The state and predictability of the art

It is well established that "the scope of enablement varies with the degree of unpredictability of the factors involved", and physiological activity is considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved); *Nationwide Chemical Corporation, et. al. v. Wright, et. al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances); *Ex parte Sudilovsky* 21 USPQ2d 1702 (Applicant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable).

The prior art (see Gharat et. al., Expert Opinion on Therapeutic patents (2008) 18:159-208) teaches a large variety of agonists and antagonists of the vanilloid receptor (see sections 2 on page 160 and 3 on page 161). Many of these structures resemble the structure of capsaicin (see compound 1 on page 160 and compounds 3 through 8 on page 163). Then they disclose several families of TRPV1 antagonists: from Pyridyl piperazine carboxamides (see section 3.2 on page 164), 1,3-disubstituted ureas (see section 3.5 on page 166), aryl cinnamides (see section 3.6 on page 192), but there are no close related structures to the ones claimed in the instant application.

4. The breadth of the claims

Claims 27 and 28 recite a broad genus of compounds listed in claim 1.

5. The amount of direction or guidance provided and the presence or absence of working examples

MPEP 2164.03 cites: "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the

nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology."

The specification teaches that Vanilloid receptors (also known as capsaicin receptors) play an important role in pain and inflammation. VR1 agonists have been used as topical anesthetics. However, agonist application may itself cause burning, pain, which limits this therapeutic use. The specification teaches that VR1 antagonists are desirable for the treatment of chronic and acute pain (see page 3). Among those compounds the specification discloses compounds of general formula I as potential VR1 antagonists (see page 4). The specification then recites that some of these compounds exhibit Ki of no greater than 1 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in a capsaicin receptor binding assay and/or have an EC50 or IC50 value no greater than 1 micromolar, 100 micromolar, 100 nanomolar, 50 nanomolar, 10 nanomolar or 1 nanomolar in an assay for determination of capsaicin receptor antagonist activity (see page 5, lines 5-9), but no specific data (see discussion below). The specification further provides the description of several assays including a Capsaicin Receptor Binding Assay (see example 3 on page 46), but it appears to be

silent on a nexus between any specific compound of formula I and its binding activity. The specification further provides the synthetic procedure and structure for only 5 close related compounds (see pages 43-45). These five compounds show a very narrow set of substituents for Z, W, Y, Ar1 and Ar2 (for example Ar1 is either trifluorophenyl or trifluoropyridyl, Ar2 is a para substituted phenyl ring, and Z = W = Y = C-H) and as mentioned before no binding data is provided for these compounds. In other words, the specification only discloses the structure of five compounds and appears to be silent regarding the binding activity of any of these compounds.

6. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept that instantly claimed genus of compounds listed in claim 1 (except for the compounds listed in Table I (see specification, pages 44-45)) could be predictably used for inhibiting binding of a vanilloid ligand to a capsaicin receptor *in vitro* or *in vivo*.

Determining if any particular claimed compound would inhibit the binding of a vanilloid ligand to a capsaicin receptor (except for those listed in Table I) would require exploring new synthetic procedures (see discussion below) and screening in a binding assay. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 27-28 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Claims 1-2, 5, 7-9, 11, 16, and 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compounds listed in Table I (see specification, pages 44-45), does not reasonably provide enablement for the remaining compounds claimed in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention</u>

Claims 1-2, 5, 7-9, 11, 16, and 48-51 recite a compound represented by the general structure represented in claim 1 or a pharmaceutical composition comprising a compound of claim 1.

2. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

3. The state and predictability of the art

Since the compounds of claim 1 are novel there is no synthetic procedure for these particular compounds in the prior art.

It is well know in the prior art that organic synthesis is still an experimental science. Even though the knowledge of organic synthesis and the arsenal of chemical reactions have exploded in the last decades, there is still a high degree of unpredictability in organic synthesis. See for example Dorwald F. A. (Side reactions in organic synthesis, 2005, Wiley, VCH, Weinheim, pg. IX of Preface) where it says: " Most non-chemists would probably be horrified if they were to learn how many attempted synthesis fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working on what went wrong, and why. He later states: "The final synthesis usually looks like quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which

the development (sometimes even repetition) of a synthesis usually implies will be able to appraise such work". And finally: "Chemists tend not to publish negative results, because these are, as opposed to positive results, never definitive (and far too copious)."

4. The breadth of the claims

Claim 1 is very broad in terms of the number of compounds claimed.

5. The amount of direction or guidance provided and the presence or absence of working examples

MPEP 2164.03 cites: "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful

teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology."

Applicant provides a synthetic procedure for some of these compounds (see schemes 1, 2 and 3 on pages 25-26, and example 1 on pages 41-43). However, even though applicant claims an extensive and diverse set of substituents for Ar1, Ar2, Y, W, and Z; the actual compounds disclosed (5 total, see Table 1, pages 44-45) show a very narrow and defined set of substituents: for example Ar1 is either trifluorophenyl or trifluoropyridyl, Ar2 is a para substituted phenyl ring, and Z = W = Y = C-H. The general structure of claim 1 encompasses millions of compounds with a large and diverse set of substituents like: 5 to 10-membered aromatic carbocycles and heterocycles. For example, there is no clear reference or synthetic procedure for the case wherein W = Y = Z = N. Although the synthetic procedures described do enable for certain core structures like when W = Y= Z = Carbon, they do not enable for all possible combinations claimed in the instant application.

6. The quantity of experimentation necessary

As discussed above (see: 3. the state and predictability of the art), small changes in the structure of one of the reagents could cause a completely different synthetic outcome (i.e. different products, lower yields or no reaction at all). Based on this, and since applicant claims such a diverse set of substituents like aromatic carbocycles and

heterocycles (see: 5. The amount of direction or guidance and the presence or absence of working examples above) it is expected that some, if not most of the A1, Ar2, W, X and Z substituents recited in claim 1 (except for those specifically listed in claims Table I on pages 44-45) will not provide the desired synthetic outcome outlined by applicant in pages 41-43 (schemes 1, 2 and 3) or example 1 on pages 41-43.

So, determining how to make a particular compound with an Ar1, Ar2, W, Y, and Z group not included in Table I would require testing new synthetic pathways for the different compounds. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 1-2, 5, 7-9, 11 16, and 48-51 do not comply with the enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is

(571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
October 14, 2008

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642